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EXAMINER	
WEN, SHARON X	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,207	TAMURA ET AL.	
	Examiner	Art Unit	
	Sharon Wen	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *4,7,8,12 and 17-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-11,13-16 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 07/20/2007 have been entered.
Claims 1-51 are pending.

2. Given Applicant's election of methods of treating previously not present and presentation of newly amended claims, the following Groups have been set forth for the restriction

Election/Restrictions

Group I, claim(s) 1-16 and 49-51, drawn to a method of preventing or treating arthritis, comprising administering to a patient an antibody which specifically binds to FGF-8.

Group II, claim(s) 17-32, drawn to a diagnostic agent comprising an antibody which specifically binds to FGF-8.

Group III, claim(s) 33-48, drawn to a diagnostic method for judging arthritis comprising detecting and/or determining FGF-8 using an antibody which binds to FGF-8.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 for reasons stated in the previous Restriction Requirement, mailed 06/20/2007, and reiterated herein for Applicant's convenience.

The uniting feature of the present invention is the antibody that binds FGF-8. Hanai et al. teaches an anti-FGF-8 antibody (U.S. Patent 5,952,472). Therefore, the uniting feature of the present invention does not contribute over prior art; hence no special technical feature exists.

3. Applicant's election of the methods of claims 1-16 and 49-51; species an anti-FGF-8 antibody without amino acid substitution; species SEQ ID NOs: 18, 21 and 7-12 regarding the antibody heavy and light chain variable regions and the corresponding CDRs; and species KM8037 (FERM BP-8084) as the transformant that produces the antibody in Response to Election/Restriction filed on 07/20/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4, 7, 8, 12 and 17-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions, there being no allowable generic claim.

Claims 1-3, 5-6, 9-11, 13-16 and 49-51 are currently under examination as they read on a method of preventing or treating arthritis, comprising administering to a patient an antibody which specifically binds to FGF-8, wherein the antibody is without amino acid substitution, comprises SEQ ID NOs: 18, 21 and 7-12 regarding the antibody heavy and light chain variable regions and the corresponding CDRs, and is produced by KM8037 (FERM BP-8084) transformant.

Priority

4. The domestic priority date for claims 1-3, 5-6, 9-11, 13-16 and 49-51 is deemed the filing date of PCT/JP02/13650, i.e., 12/26/2002.

Applicant's claim for foreign priority is acknowledged. Certified copies of foreign priority application, 2001-400677, submitted under 35 U.S.C. 119(a)-(d), have been placed of record in the file. The support for Applicant's claim for foreign priority cannot be determined because application 2001-400677 is in Japanese and no certified translation has been provided.

Applicant is invited to amend the first line of the specification to reflect Applicant's claim for domestic priority.

Information Disclosure Statement

5. Applicant's IDSs filed 06/28/2004, 09/21/2004 and 04/13/2006 are acknowledged and have been considered.

Specification

6. Applicant is requested to review the application for the spelling error, use of trademarks, embedded hyperlinks and/or other form of browser-executable code (e.g. see page 4 line 20 of specification).

Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference.

Claim Rejections - 35 USC § 112 second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3, 5, 6-11, 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 and dependent claims thereof are indefinite in the recitation of "an antibody fragment thereof". As the specification does not provide a definition for the term "an antibody fragment thereof", one of skill in the art is not reasonably apprised of the metes and bounds of the antibody fragment because the term "an antibody fragment thereof" includes non-antigen-binding portions and antigen-binding portions of an antibody.

For the purpose of examination, the term "an antibody fragment thereof" reads on an antigen-binding fragment thereof.

Applicant is invited to amend the claims accordingly to obviate this rejection.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add New Matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 5-6, 9-11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) **The following Grounds of Rejection pertain to an antibody with fewer than all 6 CDRs.**

Claims **11** and **13** recite three CDRs of the heavy chain variable region or the light chain variable region.

The breadth of the instant claims encompasses an anti-FGF8 antibody with only three CDRs found in either the heavy chain or the light chain.

The specification discloses that anti-FGF8 antibody with complete viable domains with six CDRs for both heavy chain and light chain (e.g. see pages 10 of the instant specification).

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids sequences recited in the instant claims. A person skill in the art would not be able to predict which additional CDRs are to be paired together to form a functional anti-FGF8 antibody.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function.

For example Rudikoff et al. (PNAS 1982, 79:1979-1983) teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see entire document, particularly page 1979).

Further, The state of the art at the time the invention was made recognizes even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function.

For example, Rader et al. (PNAS 1998, 95:8910-8915) teach in vitro selection and evolution of antibodies derived from phage display libraries by paring either heavy or light chain of the rodent antibody with human polypeptide library for antibody humanization is unpredictable, and certain antibodies cannot be humanized using this approach; and in addition, antibodies consisting of the same heavy chain paired with light chains that differ in light chain CDR3 and elsewhere in VL can obtain undesired feature of binding different epitopes of the same antigen (see entire document, particularly Discussion on pages 8914-8915). Rader et al. methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domain.

Furthermore, Rader et al. conclude that therapeutic antibodies that are unreactive to the antiidiotypic response would allow therapy to continue and introduction of modest changes within the variable domain of an antibody can dramatically alter its reactivity to an antiidiotypic response.

Therefore, it is unlikely that the antibodies as defined by the claims, which contain only three CDR3 in either heavy or light chain would have the required binding function and functional limitations such as specifically binds and inhibit activity of FGF-8. The specification provides insufficient direction or guidance regarding how to produce antibodies as broadly defined by the claims other than the antibody with all six CDRs for both heavy and light chain. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention using the antibody with only three CDRs.

B) **The following Grounds of Rejection pertain to "preventing" arthritis.**

Claims **1-3**, **5-6**, **9-11** and **13-16** are directed a method of preventing arthritis comprising administering an anti-FGF-8 antibody. The specification provides enabling disclosure for using anti-FGF-8 antibody in arthritis mouse and rat models (see Examples 7-8 on page 106-117 of the specification). The specification does not provide sufficient *in vivo* or *in vitro* evidence showing anti-FGF-8 antibody can prevent arthritis as claimed in claim 1, nor does the specification provide sufficient enabling evidence for preventing other disease including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, ankylotic arthropathy, psoriatic arthritis, intervertebral disc disease, acute crystalline synovitis (gout, pseudogout) and the like as disclosed on page 72 of the specification.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively prevent any disease or reach any therapeutic endpoint in humans by administering the antibody. The specification does not teach how to extrapolate data obtained from in vitro or in vivo inhibition of FGF-8 activity (see, e.g., Example 1 on page 98 of specification) to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the antibody exemplified in the specification or the method of treating using the antibody, encompassed by the claims.

According to *The Merck Manual of Diagnosis and Therapy*, the precise causes of rheumatoid arthritis, a species of arthritis disclosed in the instant specification (see page 72 of the specification), is unknown. While many factors, such as smoking or viral infections, are thought to play a role, a genetic predisposition has been identified in a certain population to contribute to the chronic autoimmune manifestation (*The Merck Manuals Online Medical Library,* [online]. Whitehouse Station, NJ: Merck Research Laboratories, 2006-2007. [retrieved on 10/10/2007]. Retrieved from the Internet: < URL:http://www.merck.com/mmpe/print/sec04/ch034/ch034b. html>. Rheumatoid Arthritis (RA), see pages 1-9). However, the instant disclosure does not provide sufficient in vitro or in vivo evidence showing the administration of an anti-FGF-8 antibody can counter-act the cause or the manifestation of rheumatoid arthritis as defined by *The Merck Manual of Diagnosis and Therapy* in order to prevent the disease.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Immunomodulation is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as rheumatoid arthritis targeted by the claimed invention (see pages 26 of the instant specification).

The instant application provides insufficient guidance and instruction on the necessary steps one of skill would need to administer the antibody and achieve the intended results, i.e. preventing arthritis. In view of the unpredictability of the art and insufficient working examples provided by Applicant of administering an anti-FGF-8 antibody for therapy, it would require undue amount of experimentation for a skilled artisan to practice the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

In regard to the recitation of "preventing", Applicant is invited to amend the claims to avoid the recitation of "preventing" to obviate this rejection.

C) **The following Grounds of Rejection pertain to biological deposit.**

Claim **15** is rejected for failing to enable one of skill to make or use the claimed invention.

It is apparent that transformant **KM8037** is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line or hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Although Applicant disclosed that KM8037 was deposited as FERM BP-8084 in International Patent Organism Depositary, National Institute of Advanced Industrial Science and Technology (AIST Tsukuba Central 6, 1-1-1 Higashi, Tsukubashi Ibaraki, 305-8566, Japan) on Jun. 20, 2002 (see page 154 of the specification) there appears no assurances indicated above. Applicant's provision of these assurances would obviate this rejection.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-3, 5-6, 9-10, 16 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baird et al. (U.S. Patent 6,037,329) in view of Hanai et al. (U.S. Patent 5,952,472) and Owen et al. (*Journal of Immunological Methods*, 1994, 168:149-165).

The instant claims are directed to a method of treating arthritis comprising administering an anti-FGF-8 antibody to inhibit activity of FGF-8, wherein the antibody is a monoclonal, humanized, i.e., human chimeric or human CDR-grafted, or a fragment thereof.

Baird et al. teach a method of treating arthritis, in particular, rheumatoid arthritis, comprising administering an inhibitor of FGF-8 (see entire document, in particular, see column 10, last paragraph; column 25, first full paragraph; column 47, last full paragraph; and column 48, first full paragraph). The inhibitor of FGF-8 taught by Baird et al. is an antisense molecule (see column 25, first full paragraph).

Baird et al. does not teach using an anti-FGF-8 antibody as an inhibitor of FGF-8 to treat arthritis. However, anti-FGF-8 antibodies are well known in the art at the time of the invention was made as demonstrated by Hanai et al. (see entire document).

Hanai et al. teach monoclonal antibody that can neutralize the FGF-8 activity (see entire document, in particular, see column 2, lines 9-10). In addition, Hanai et al. teach using the anti-FGF-8 monoclonal antibody which is produced from a hybridoma to treat diseases (see Background and Summary of the Invention in columns 1-2).

Given the teachings of the two references, it is *prima facie* obvious to one of ordinary skill in the art, at the time of filing of the instant application, to substitute the anti-FGF-8 antibody as taught by Hanai et al. for the FGF-8 antisense molecule in the method of treating arthritis as taught be Baird et al. for the same purpose of treating arthritis.

An ordinary artisan would have been motivated to substitute the anti-FGF-8 antibody for antisense molecule to treat arthritis given the teaching by Baird et al. stating that there are problems associated with gene therapy, and that there is a compelling need for improved treatments (see column 2, first paragraph) and the teaching by Hanai et al. suggesting that the antibody having a neutralization activity specifically against FGF-8 would be effective in treating disease (see column 1, third paragraph).

Even though the combined teachings of Baird et al. and Hanai et al. are silent on "inhibiting joint destruction", "protecting cartilage", or "inhibiting growth of synovial membrane" (claims 49-51), given that the combined teachings render the claimed method of treating arthritis comprising administering an anti-FGF-8 antibody *prima facie* obviouse, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Therefore, one of ordinary skill would recognize that the same method steps comprising administering the anti-FGF-8 antibody would also be able to inhibit joint destruction, protect cartilage or inhibit growth of synovial membrane.

Baird et al. and Hanai et al. do not teach a humanized, i.e., human chimeric or human CDR-grafted antibody or the antigen binding fragments thereof. However, it is well known in the art, at the time of filing, to humanize antibodies or obtain the antigen-binding fragments thereof for therapeutic purposes in human as demonstrated by Owens et al. (see entire document).

In particular, Owens et al. teach the methods of making human chimeric antibodies and human CDR-grafted antibodies from rodent monoclonal antibodies (see pages150-155). Moreover, Owens et al. teach the construction of antigen-binding fragments, in particular, F(ab')2, Fab, Fv and scFV, which read on a "CDR-containing peptide" (claim 16) (see Owens et al., pages 155-157).

Given the combined teachings of Baird et al. and Hanai et al., in view of Owens et al., it is prima facie obvious to one of ordinary skill in the art, at the time of filing of the instant application, to substitute the anti-FGF-8 antibody as taught by Hanai et al. for the FGF-8 antisense molecule in the method of treating arthritis as taught be Baird et al. for the same purpose of treating arthritis, wherein the antibody is human chimeric, human CDR-grafted or antigen-binding fragments thereof as taught by Owens et al.

An ordinary artisan would have been motivated to humanize the antibody according to the methods taught by Owens et al. because Owens et al. teach a need for humanizing rodent monoclonal antibodies due to problems associated with using the rodent monoclonal antibodies in human therapy and advantages associated with using antigen binding fragments thereof, i.e., shorter half-lives in vivo (see Introduction on page 149).

Therefore, the invention, as a whole, was *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Wen whose telephone number is (571) 270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Wen, Ph.D.
Patent Examiner
October 11, 2007

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10/11/07